

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee
QUESTIONS
February 8, 2011

Accelerated Approval & Oncology Experience

The Oncologic Drug Advisory Committee will discuss the accelerated approval process. To focus the discussion, the following non-voting questions will be posed to committee members. The first question pertains to studies supporting the initial accelerated approval. The remaining questions apply to post-marketing studies designed to confirm clinical benefit.

1. SINGLE ARM TRIALS TO GAIN ACCELERATED APPROVAL

Single arm trials have formed the basis for 29/49 or over half of the accelerated approvals for oncology drugs to date. While single arm trials often require less resources and time to complete, they provide limited data on clinical benefit and safety. Single arm trials for accelerated approval have usually been performed in refractory populations where no available therapy exists. As a greater number of drugs are approved, identification and documentation of a refractory population is increasingly problematic. In addition, marginal response rates observed in single arm trials in a refractory setting make it difficult to determine whether the findings are “reasonably likely” to predict clinical benefit.

Alternatives to a single arm trial in a refractory population include randomized trials in a less refractory population against an active control using a surrogate endpoint analyzed at an earlier time point or a randomized trial in a refractory population comparing the investigational agent to best supportive care or various agents selected by investigators. Randomized trials provide the opportunity to look at a wider variety of endpoints and allow for an improved characterization of safety.

DISCUSS: Given the problems with single arm trials, discuss scenarios where a randomized study should be required for accelerated approval. Alternatively, please discuss situations where single arm trials may be appropriate to support an accelerated approval.

2. NUMBER OF CONFIRMATORY TRIALS

The time from either successful completion of a required post-marketing study or withdrawal of the indication can be prolonged. For drug approval in most therapeutic areas outside of oncology, two well-designed randomized trials are usually required. In oncology, the FDA has frequently approved drugs on the basis of a single well-conducted trial. The FDA usually receives proposals for a single trial to be conducted post-approval to demonstrate clinical benefit for drugs receiving accelerated approval. However, in the setting of accelerated approval, when only one confirmatory post-marketing trial is conducted, there is the increased risk that clinical benefit will not be demonstrated in a timely manner if that single

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trial fails to confirm a benefit or does not accrue patients as rapidly as planned. This may lead to either withdrawal of the indication or the need to conduct a second trial, resulting in substantial delays.

DISCUSS: Discuss whether applicants should be required to conduct at least two adequate and well-controlled clinical trials as their accelerated approval commitment to verify clinical benefit.

3. TIMING OF CONFIRMATORY TRIALS

Accelerated approval regulations clearly state that post-marketing trials “**would usually be underway at the time of accelerated approval.**” Once a drug gains accelerated approval in a refractory disease stage, accrual to a confirmatory trial in the same setting is difficult. Pursuing a confirmatory clinical trial in a less refractory setting can potentially circumvent this problem. However, changes in science, accrual challenges and other hurdles may lead to delays. The FDA believes that more timely completion of accelerated approval confirmatory trials can be enhanced if accelerated approval is granted when the confirmatory trial is on-going.

DISCUSS: Given the regulations state that confirmatory trials would usually be underway at the time of accelerated approval, discuss whether an approval should be delayed until such trials are ongoing, keeping in mind that access to not yet marketed drugs could be accomplished under expanded access programs if a delay is anticipated.

4. THE USE OF COOPERATIVE GROUPS TO CONDUCT CONFIRMATORY TRIALS

The FDA recognizes that cooperative groups, both in the United States and Europe, are critical to drug development and encourages their participation throughout the drug discovery process.

Applicants may engage a cooperative group to design and execute a confirmatory trial to fulfill their regulatory obligation. However, the ultimate responsibility of completing the confirmatory trial with due diligence rests with the applicant. This fact may hold added importance to sponsors with the introduction of substantial financial penalties (2007 FDAAA) for lack of timely completion of these trials at the agreed upon dates.

DISCUSS: Please discuss the use of a cooperative group to conduct the trial(s) required to demonstrate clinical benefit to fulfill their accelerated approval obligation. If a cooperative group is used, discuss whether an additional trial(s) should be conducted under the direct supervision of the applicant to ensure adherence to completing post marketing requirements by a specified date.